European Medicines Agency

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CONCEPT PAPER ON PREPARATION OF AN ADDENDUM TO THE GUIDELINE ON DEVELOPMENT OF ANTIBACTERIAL AGENTS TO SPECIFICALLY ADDRESS THE CLINICAL DEVELOPMENT OF NEW AGENTS TO TREAT TUBERCULOSIS

AGREED BY EWP	April 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	26 April 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2007

The proposed guideline will be an addendum to: Guideline on the evaluation of medicinal products indicated for treatment of Bacterial Infections (CPMP/EWP/558/95)

Comments should be provided to EWPSecretariat@emea.europa.eu
Fax +44 20 7418 86 13

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

There are several new antibacterial agents currently at various stages of development that are intended for the treatment of *Mycobacterium tuberculosis*. Some of these agents are truly novel and may be developed only for treating mycobacterial infections while others have been or may be developed additionally for the treatment of other types of bacterial infections.

Much of the guidance provided in CPMP/EWP/558/95 rev 1 is relevant to the evaluation of antibacterial agents in the treatment of tuberculosis (TB). However, there are some special issues for the study of the safety and efficacy of treatments for tuberculosis that are not addressed in the current guideline. This concept paper considers the need for an addendum to the existing CHMP guideline on the clinical development of antibacterials to cover matters that are specific to novel anti-TB agents.

2. PROBLEM STATEMENT

In contrast with the vast majority of bacterial infections *Mycobacterium tuberculosis* is currently treated with combination therapy and for many months. The choice of regimen and its duration depends on the characteristics of the disease (e.g. localised or disseminated to certain sites), the resistance profile of the organism, the potential for drug interactions (a particular potential difficulty in those co-infected with HIV) and the ability of patients to tolerate certain agents. Complex regimens and/or high pill burdens are also a concern for patient compliance. Clearly simpler and shorter regimens, ideally with less potential for drug interactions and better tolerability, are needed for the management of tuberculosis. In addition, there is now a need for new regimens with activity against multi-drug-resistant (MDR-TB) and extended MDR (XDR-TB) *M. tuberculosis* infections. MDR-TB takes longer to treat and therapy has to employ second-line drugs, which may have more side effects. XDR-TB is resistant to first- and second-line drugs and so the treatment options are seriously limited.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

There are several issues for the design of clinical studies and the overall clinical development programme for new agents intended to treat tuberculosis that are not adequately covered by the current CHMP guideline on the clinical development of antibacterial agents. Some of the additional matters that need to be covered in an addendum are listed in section 4 below. Such guidance is now needed since there are several new agents at various stages of clinical investigation. EU Regulatory Agencies have already been approached for detailed advice and it is very likely that CHMP will be asked for scientific advice in the near future. Therefore, the development of EU guidance would be helpful to regulators and sponsors alike.

4. RECOMMENDATION

The Working Party recommends the preparation of an addendum to the CHMP Guideline on the Clinical Evaluation of Antibacterial Agents (CPMP/EWP/558/95 rev 1) to address issues of particular relevance to the development of new agents to treat tuberculosis.

The points that should be addressed include (but are certainly not limited to):

- Potential use of PK/PD relationships to help predict dose regimens.
- Potential use of early bactericidal activity (EBA) in dose-finding studies to aid the rational selection of appropriate TB dosage regimens to use in pivotal trials.
- Potential for any extrapolation that might be allowed between the composite regimen(s) in which the new agent has been studied and other possibly useful regimens.
- Clinical trial design issues for evaluating a new agent in treating MDR-TB and XDR-TB, including the choice of appropriate control regimens.
- Implications for study design and for the ultimate prescribing information if the novel agent has to be co-administered with at least one other novel agent to adequately treat XDR-TB.

- Potential need for separate studies for certain types of TB depending on the localised or disseminated nature of the infection and the exact sites involved (e.g. meninges and bone).
- Demonstration of the contribution of an individual agent to an overall regimen.
- Evaluation of the appropriate total duration of therapy.
- The choice and definition of endpoints that might be used alongside more traditional endpoints (e.g. serial sputum colony counts [SSCC]).
- Duration of follow-up.
- Diagnostic criteria (e.g. special difficulties in children).
- Evaluation of the safety profile of a novel agent when used in different combination regimens.
- Potential need for studies in specific patient groups (e.g. co-infection with HIV, treatment with TNF-α antagonists).

5. PROPOSED TIMETABLE

First draft to Anti-Infectives Drafting Group September 2007. Meeting October/November 2007
Second draft to Anti-Infectives SAG and consultation with SAG November/December 2007
Third draft released for 3-month consultation January 2008
Deadline for comments April 2008
Rediscussion in EWP May 2008
Expected date for adoption by the Committee June/July 2008

Although this timetable is somewhat lengthy it does mean that a draft document would be in the public domain early next year.

6. RESOURCE REQUIREMENTS FOR PREPARATION

In the first instance it is suggested that an Anti-Infectives drafting group, including as far as possible the persons who participated in the drafting group that prepared CPMP/EWP/598/95 rev 1) should meet to discuss an initial draft to be prepared by an appointed person. After first amendments have been made it is recommended that specific input to this draft should be obtained from the Anti-Infectives SAG, including additional experts to be drafted in who are particularly experienced in the management of tuberculosis and conduct of clinical studies.

7. IMPACT ASSESSMENT (ANTICIPATED)

Guidance is needed since there are several new agents at various stages of clinical investigation. EU Regulatory Agencies have already been approached for detailed advice. Therefore, the development of EU guidance would be helpful to regulators and sponsors alike.

8. INTERESTED PARTIES

WHO (http://www.who.int/tb/strategy/en/)
"The Stop TB Strategy: The new six-point strategy, developed by WHO over a two-year period, builds on the successes of DOTS while also addressing the key challenges facing TB control in providing access to TB treatment and care, including TB/HIV and MDR-TB patients. The new strategy also seeks to strengthen health systems, engage all care providers, empower people with TB and communities, and promote research."

Stop Tb Partnership (http://www.stoptb.org/)
"The Stop TB Partnership was established in 2000 to realize the goal of eliminating TB as a public health problem and, ultimately, to obtain a world free of TB. It comprises a network of international organizations, countries, donors from the public and private sectors, governmental and nongovernmental organizations and individuals that have expressed an interest in working together to achieve this goal
WHO has a dual role in the Stop TB Partnership. As a leading agency in the partnership, WHO provides guidance on global policy and has permanent representation in the Stop TB Coordinating Board. WHO is also the housing institution of the Stop TB Partnership Secretariat, which benefits from the mechanisms of WHO. The secretariat follows the rules and regulations of WHO for its

administrative, financial and human resources management, subject, if necessary, to the adaptations which might be required in order to meet the particular needs of the Stop TB Partnership".

Global Alliance for Tb Drug Development (http://new.tballiance.org/home/home-live.php)
"Since its formation in 2000, the non-profit TB Alliance has built the largest pipeline in history of potential new drugs for the treatment and cure of tuberculosis, a disease that kills someone every fifteen seconds"

International Union Against Tuberculosis and Lung Disease
(http://www.iuatld.org/index_en.phtml)
"The Union is a non-profit, non-governmental voluntary organization, founded in 1920. Its members, organizations and individuals throughout the world are dedicated to the prevention and control of tuberculosis and lung disease, to disseminating information about the hazards of smoking and to the promotion of overall community health".

Various international and national Societies specific to Thoracic Medicine, Infectious Diseases and HIV.